

REMARKS

This paper is submitted in response to the Notice of Non-Compliant Amendment mailed on April 14, 2011 to correct an informality and label new claim 58 with a status identifier. Additionally, this paper is filed in Response to the Office Action mailed December 10, 2010. Claims 27 to 32, 34 to 43 and 48 to 54 are under consideration. New claims 55 to 59, directed to the elected invention have been added. Accordingly, claims 27 to 32, 34 to 43 and 48 to 59 are under consideration.

Applicants respectfully request an interview with the Examiner of sufficient duration to discuss all grounds for rejection that may remain upon consideration of this paper and the accompanying documents submitted herewith.

The Amendment to the Specification

The specification has been amended to correct an informality. In particular, the specification has been amended to correct the date for the deposited biological material, the SAM-6.10 antibody producing hybridoma. As evidenced by the accompanying Revised Statement under 37 C.F.R. §1.804(b) executed by Dr. Frank Hensel, Applicants had possession of the hybridoma that produces SAM-6.10 antibody and the SAM-6.10 antibody heavy and light chain variable region sequences referenced in the application, for example, at page 13, lines 8-9, at the time the application was filed.

Thus, the amendment was made to address an informality no new matter has been added. Accordingly, entry thereof is respectfully requested.

The Claim Amendments

The claim amendments are supported throughout the specification. In particular, the amendment to claims 27 and 43 to delete reference to a specific light chain (V_L) variable region sequence (SEQ ID NO:1) is supported, for example, by originally filed claims 1 and 2, at page 7, second and third paragraphs, the paragraph bridging pages 8 and 9, and at page 9, second paragraph. The amendment to claim 52 to recite "or" is supported, for example, by original claim 17, at page 7, second and third paragraphs, and the paragraph bridging pages 8 and 9. Thus, as the claim amendments are supported throughout the originally filed specification, no new matter has been added and entry thereof is respectfully requested.

The New Claims

Claims 55 to 59 are supported throughout the specification. In particular, claims 55 to 59 are supported, for example, by originally filed claims 1 and 2, at page 7, second and third paragraphs, and at page 9, second paragraph. Thus, as claims 55 to 59 are supported throughout the originally filed specification, no new matter has been added and entry thereof is respectfully requested.

Exhibit C

Attached for the Examiner's consideration are selected pages from PCT WO 2010/088739 (a complete copy is submitted in the accompanying IDS). Applicants note that PCT WO 2010/088739 discloses, among other things, variant antibodies, antigen identities, and studies of variant antibody binding to target cells that express antigen to which SAM-6 antibody binds (Exhibit C, Examples 13-19). Notably, the attached include a description of binding studies demonstrating that SAM-6.10 (aka SAM-6) ScFv, sequence variants and a heavy chain variable region sequence alone (VH alone, SEQ ID NO:3) without a light chain variable region sequence, have binding activity for apolipoprotein B100, LDL, VLDL and/or deglycosylated LDL (Examples 13 and 19). In particular, ELISA analysis revealed that ScFv SAM-6, SAM-6 sequence variants and a heavy chain variable region sequence SAM-6 VH alone (SEQ ID NO:3) without any light chain variable region sequence binds to apolipoprotein B100 (Exhibit C, page 99). Accordingly, Applicants respectfully request consideration of the accompanying binding data.

Objections to the Figures

The Examiner has maintained that the Descriptions of Figures 1 and 2 allegedly are unclear, namely for lacking units for the y-axis label.

Applicants respectfully point out that the data in Figures 1 and 2 would be understood by one of skill in the art in view of the description of the two respective figures in the specification at pages 19-20.

In particular, in the paragraph bridging pages 19-20, the description states that "Figure 1 shows the measurement of oxLDL in dependence on the incubation time," and that "in the experiment, LDL...was oxidized for 3 and 15 h," and that "the amount of oxidized LDL increases with increasing incubation time." The y-axis of both Figures 1 and 2 show increasing values of "0.2," "0.4," etc. Consequently, the y-axis obviously reflects the LDL

oxidation, which increases with increasing incubation time as reflected by the longer bars and as described in the Figure descriptions. Thus, the amount of LDL and units are not necessary to understand that more oxidized LDL is present (again as reflected by the longer bars) with increasing oxidation time from 0, to 3 to 15 h. Consequently, the data represented in Figure 1 showing increased LDL oxidation over the indicated time periods would be understood by one of skill in the art.

In terms of the assertion that “Figure 2 cannot be evaluated because there is no distinction between the kontrolle and SAM-6 as the bars are both open,” at page 20, second paragraph, the description states that “Figure 2 shows the proof of binding of SAM-6 to oxLDL,” and that “the result shows that the more LDL that is present in its oxidized form, the more strongly the antibody SAM-6 according to the invention binds,” which is indicated by longer bars at each respective time point. At page 20, second paragraph, the description also states that “the ELISA plate was precoated with LDL fractions oxidized to different degrees,” which as stated in the Figure 1 description is indicated by the 0, 3 and 15 h time points along the x-axis and the longer bars reflecting increased LDL oxidation. Consequently, obviously one of skill in the art based upon the foregoing description understands that the longer bars at each successive time point in Figure 2 reflect SAM-6 binding (i.e., “the more LDL that is present in its oxidized form, the more strongly the antibody SAM-6 according to the invention binds”), and the shorter bars in which there is little apparent change reflect control (i.e., Kontrolle). Consequently, the data represented in Figure 2 would be clear to one of skill in the art.

Furthermore, the Examiner requests submission of new drawings “with the axes properly labeled and unites clearly identified for each figure.” However, as much as Applicants would like to comply, the submission of such new figures would likely constitute addition of new matter, particularly since the Examiner believes that the figures are deficient and the submission of the proposed revised figures would require additional information in order to rectify the alleged deficiencies. For this reason alone, Applicants respectfully cannot submit new drawings as requested by the Examiner since doing so would potentially introduce new matter.

In any event, the data represented by Figures 1 and 2 would generally be understood by one of skill in the art: the Figures show relative differences that would be readily understood by one of skill in the art, and the USPTO does not require that Figures be represented in a particular format, let alone illustrate units or that a scale or statistical

information be included. Moreover, Figures 1 and 2 are not essential to a technical understanding of the invention or to evaluate patentability of the claims.

In view of the foregoing remarks, the data represented by Figures 1 and 2 in combination with the description of the data in the as-filed specification would be sufficiently clear to one of skill in the art. Consequently, Applicants respectfully request that the objection to the specification be withdrawn.

Objection to the Substitute Sequence Listing and Specification

The Substitute Sequence Listing and amendment to the Specification previously submitted to correct errors in the sequences stands objected to due to the addition of allegedly new matter, namely the correction of 2 incorrect amino acid residues in SEQ ID NO:3 from Lys-Thr to Arg-Pro. Allegedly, there is no written description to support the amendment to correct the sequence error

Applicants respectfully point out that this issue was squarely and unambiguously addressed by the court in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002). In particular, the court held “that reference in the specification to a deposit may also satisfy the written description requirement with respect to a claimed material,” and that “reference in the specification to deposits of nucleotide sequences describe those sequences sufficiently to the public for purposes of meeting the written description requirement.” *Id.* at 965 and 970. In view of the fact that deposited sequences satisfy the written description requirement for those sequences, the referenced deposited biological material (DSM ACC2903) in the specification adequately describes the recited heavy (SEQ ID NO:3) and light chain (SEQ ID NO:1) variable region sequences. Accordingly, the previously filed Substitute Sequence Listing and amendment to the Specification correcting the sequence error of SEQ ID NO:3 does not add new matter, and the grounds for objection must be withdrawn.

The specification also stands objected to due to alleged defects in the previously filed Statement under 37 C.F.R. §1.804(b). Submitted herewith is a Revised Statement under 37 C.F.R. §1.804(b) executed by Dr. Frank Hensel that makes a specific reference to the hybridoma that produces SAM-6.10 antibody referenced in the application (for example, at page 13, lines 8-9). Accordingly, Applicants believe that the Revised Statement remedies the

alleged defects in the previously filed Statement under 37 C.F.R. §1.804(b), and respectfully request withdrawal of the grounds for objection.

I. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH
ENABLEMENT

The rejection of claims 27 to 32, 34 to 43 and 48 to 51 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 6-14.

Applicants respectfully point out that claims 27 to 32, 34 to 43 and 48 to 51 require both light (V_L) and heavy (V_H) chain variable region sequences. Thus, given that these claims require both a light chain (V_L) variable region and a heavy chain (V_H) variable region sequences, all 6 CDRs that confer antigen binding activity are present. Furthermore, certain dependent and independent claims recite the predicted CDRs of heavy (V_H) and/or light (V_L) chain variable region sequences of SEQ ID NOs:1 and 3, which confer antigen binding specificity.

Moreover, as disclosed in previously submitted Exhibit B and corroborated by Exhibit C submitted herewith, heavy chain (V_H) variable region alone, without light (V_L) is sufficient to confer binding to target. Thus, given that all claims include a heavy (V_H) chain variable region sequence which alone is sufficient to confer binding activity, clearly antibodies and polypeptides including a variant heavy chain (V_H) variable region sequence within the scope of the claims could be readily identified without undue experimentation by routine binding studies disclosed in the specification or known to the skilled artisan.

To reiterate, as previously pointed out in the record the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention relevant to antibody structure and function allows variants that bind LDL or oxLDL to be produced and identified without undue experimentation. Here, the sequence that confers binding to LDL or oxLDL is disclosed (SEQ ID NO:3). Consequently, variants of SEQ ID NO:3 could be readily produced and screened for binding to LDL or oxLDL using routine methods.

Applicants previously described an example of identifying binding variants. Namely, in view of the high level of knowledge concerning antibody structure correlating with function as acknowledged in a prior Office Action and disclosed in the specification, and the fact that SEQ ID NOs:1 and 3 and their predicted CDRs are disclosed, the skilled artisan would therefore be able to intelligently modify sequences to produce variant antibodies by

introducing selected changes to SEQ ID NOs:1 or 3, and then verify which antibodies bind to LDL or oxLDL, for example. Such a methodology of introducing changes into a heavy or light chain variable region sequence of an antibody known to bind to LDL or oxLDL and identifying those that bind to LDL and/or oxLDL could be performed without undue experimentation at the time of the invention.

To corroborate Applicant's position, submitted herewith are pages (Exhibit C) from PCT WO 2010/088739, which provides a concrete example of identifying variant antibodies without use of any greater knowledge of antigen identity than is disclosed in the as-filed application. Applicants note that PCT WO 2010/088739 discloses, among other things, variant antibodies, and studies of variant antibody and heavy chain variable region sequence alone binding to apoB-100, VLDL, LDL, or de-glycosylated LDL. Applicants reference these specific studies from the published application as merely examples of studies that corroborate that additional knowledge of antigen identity greater than disclosed in the subject application is not essential to identify antibodies including variants that bind to LDL or oxLDL.

Significantly, the studies in Example 13 (pages 97-99) are an analysis of 4 different sequences of SAM-6 antibody (pages 87-91 of PCT WO 2010/088739 have the sequences of the variants) and heavy chain variable region sequence alone for binding to apoB-100, VLDL, LDL, and/or de-glycosylated LDL. Using conventional ELISA methods, variant antibody and heavy chain variable region sequence alone binding to apoB-100, VLDL, LDL, or de-glycosylated LDL was determined. The foregoing study is one exemplary method by which one of skill in the art could identify variant antibodies without any more knowledge of antigen or epitope identity than that which is disclosed in the as-filed application.

In addition to Example 13, the data in Example 19 (page 102) refers to a particular SAM-6 variant, which exhibited increased binding affinity for LDL. Again, binding of the variant antibody to LDL was determined without the need for additional knowledge concerning the identity of the target antigen or epitope of LDL or oxLDL.

In sum, the foregoing data convincingly demonstrate that additional knowledge greater than what is disclosed in the as-filed specification as to the identity of the target antigen or epitope in LDL or oxLDL to which the claimed antibodies bind is not essential for one of skill in the art to identify variants within the scope of the claims. Consequently, the studies corroborate that one of skill in the art could identify variants of SEQ ID NOs:1 and 3 that bind to LDL or oxLDL without undue experimentation.

Lastly, in regard to the assertion in the Office Action (page 12) that it is unclear what is the target epitope and that there are differences in lipid compositions among LDLs, as is well understood in the immunology art, antibodies typically bind to proteins due to their strong immunogenicity, and proteins are more likely to be immunogenic than lipids. Furthermore, it is well understood in the art that there are very few proteins present in LDL and oxLDL, and that LDL and oxLDL share a very limited number of proteins between them. Such proteins include Apoprotein B 100 (apoB). In fact, as stated in the Terrlink et al. publication cited by the Examiner (J. Lipid Research 45:954 (2004)): “each LDL particle contains a single copy of apolipoprotein B-100” (page 955, first column). Thus, given the fact that 1) proteins are known to be more immunogenic than lipids; and 2) there is only a single apo-B-100 in LDL, which is shared with other forms of LDL including oxLDL, clearly the number of possible epitopes to which the claimed antibodies could bind is far fewer than the Patent Office suggests. Moreover, the studies in previously submitted Exhibit B and Exhibit C submitted herewith clearly demonstrate that one of skill in the art could identify variants of SEQ ID NOs:1 and 3 that bind to LDL or oxLDL without any additional knowledge of antigen or epitope identity than that which is disclosed in the as-filed specification.

In sum, variants of SEQ ID NOs:1 and 3 that bind to LDL or oxLDL within the scope of the claims could be readily identified without any additional knowledge of antigen or epitope identity than that which is disclosed in the as-filed specification without undue experimentation, as corroborated by Exhibits B and C. Accordingly, the claims are adequately enabled under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

WRITTEN DESCRIPTION

The new grounds for rejection of claims 43 and 52 to 54 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. According to the Patent Office, allegedly the correction of 2 incorrect amino acid residues in SEQ ID NO:3 from Lys-Thr to Arg-Pro is new matter.

As discussed above, the court in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002) held “that reference in the specification to a deposit may also satisfy the written description requirement with respect to a claimed material,” and that “reference in the specification to deposits of nucleotide sequences describe those sequences sufficiently to the

public for purposes of meeting the written description requirement.” Id. at 965 and 970. In view of the fact that a deposit of sequences satisfies the written description requirement for those sequences, the referenced deposited biological material (DSM ACC2903) in the specification adequately describes the recited heavy (SEQ ID NO:3) and light chain (SEQ ID NO:1) variable region sequences. Accordingly, the amendment correcting the sequence error of SEQ ID NO:3 from Lys-Thr to Arg-Pro does not add new matter, and the rejection under 35 U.S.C. §112, first paragraph, must be withdrawn.

II. DOUBLE PATENTING REJECTION

The provisional rejection of claims 27 to 32, 34 to 42 and 48 to 54 under 35 U.S.C. §102(b), as allegedly unpatentable over claims 73, 80, 81, 106 to 112, 115, 116 and 122 to 124 of co-pending application no. 10/579,290 is respectfully traversed. Allegedly, claims 27 to 32, 34 to 42 and 48 to 54 would have been obvious in view of the conflicting claims of application no. 10/579,290.

Applicants respectfully request that the rejection be held in abeyance until such time as all other rejections are withdrawn. Applicants will at that time file a remarks traversing the rejection or a Terminal Disclaimer, as appropriate.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 27 to 32, 34 to 43 and 48 to 59 clearly and patentably define the invention, and respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

For purposes of the Interview, the Examiner is respectfully requested to contact Applicant's representative at (858) 509-4065.

Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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